IMPROVED REAGENTS FOR N-AMINATION

Cross-Reference to Related Application

[0001] This application claims priority from parent application 60/395,693 filed 11 July 2002. The contents of this document is incorporated herein by reference.

Technical Field

[0002] The invention is directed to reagents that are able to aminate nitrogen atoms and to methods to conduct amination using these reagents. More particularly, the invention is directed to a phenyl hydroxylamine which is further substituted with nitro and trifluoromethyl groups.

Background Art

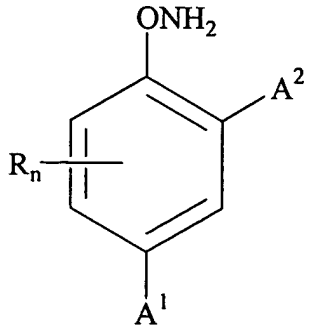
[0003] One of the reagents used to couple an amino group to a nitrogen atom recipient is 2,4-dinitro-phenyl-hydroxylamine. This reagent is effective in carrying out the reaction, but has a serious drawback in that it is quite "energetic" and poses an explosion hazard.

[0004] Boyles, D.C., *et al., Org. Proc. Res. Dev.* (2002) 6:230-233 describe a series of alternative reagents where the phenyl hydroxylamine is further substituted by a single nitro group in the para or ortho position and by halo and/or methyl groups elsewhere in the ring. These reagents were used to aminate quinazoline-2,4-diones in order to obtain antibacterial agents for toxicological studies. The contents of this document are incorporated herein by reference.

[0005] It has now been found that an improved N-amination reagent can be obtained by preparing substituted (mono-nitrophenyl)hydroxylamines which have, in addition to the nitro substituent, an additional substituent which is trifluoromethyl or CF_3.

Disclosure of the Invention

[0006] The invention is directed to compounds of the formula



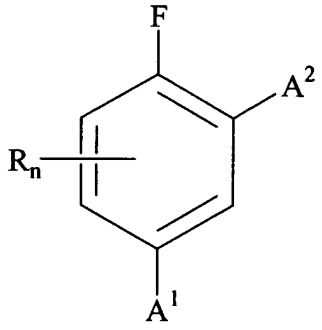
(1)

and precursors therefor, wherein at least one of A^1, and A^2 is nitro, and the other is CF_3, R is halo, alkyl, CN or CF_3 and n is 0-3. These compounds are useful in preparing products, such as those described by Boyle, *et al.* (*supra*) that contain an amino group bound to a nitrogen. These compounds may be useful in themselves as antibacterials or modulators of metabolism, or may be intermediates in the synthesis of such compounds.

[0007] In another aspect, the invention is directed to methods to aminate nitrogen atoms, especially the N of an indole moiety, which methods comprise contacting a compound, especially an indole, containing a nitrogen which is desired to be aminated with a compound of formula (1) under conditions wherein said amination occurs.

Modes of Carrying Out the Invention

[0008] The invention is directed to improved reagents for amination of nitrogen atoms. The reagents are of formula (1) as described above. These reagents can be prepared from either commercially available or synthesized starting materials using standard chemical synthetic methods. Typically, a compound of the formula



(2)

wherein A^1, A^2, R and n are as defined above, is converted to the phenyl hydroxylamine by displacement of the fluoride substituent. Thus, in one approach, the fluoride is displaced by reaction

with an alkyl hydroxyacylimidate, such as ethyl hydroxyacetimidate, in the presence of sodium hydride or another strong base in an appropriate solvent. The resulting intermediate is then treated with a strong hydrolyzing agent such as perchloric acid to yield the corresponding phenyl hydroxylamine.

[0009] In the alternative, the compound of formula (2) is reacted with Boc-hydroxylamine to obtain the corresponding -O-NHBoc intermediate which is treated with trifluoroacetic acid to obtain the desired product.

[0010] The resulting compounds of formula (1) are then used to treat suitable substrates so as to aminate them. For example, the nitrogen of an indole nucleus may be aminated by treating with the compound of formula (1) in the presence of base and a polar aprotic solvent.

[0011] The products of the amination are then useful either as intermediates for further conversion to compounds such as antibacterials, metabolite regulators, and the like. A wide variety of compounds which contain N-N linkages can be prepared using this tool.

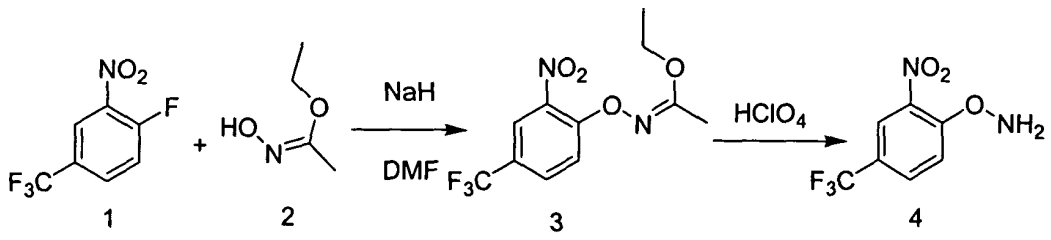
[0012] In preferred compounds, n is 0, or n is 1 and R represents CF_3 in the position ortho to ONH_2.

[0013] However, in addition to CF_3, R may also represent alkyl, halo or CN. "Alkyl" refers to straight chain, branch chain or cyclic substituent containing 1-6C such as ethyl, n-propyl, cyclohexyl, and the like. Halo refers to fluoro, chloro, bromo or iodo. Chloro is preferred. In general, it is preferred that n=0 or n=1 and, when n=1, R is present in the position ortho to the hydroxylamine substituent.

[0014] The following examples are intended to illustrate but not to limit the invention.

Example 1

Synthesis of 2-nitro-4-(trifluoromethyl)phenylhydroxylamine



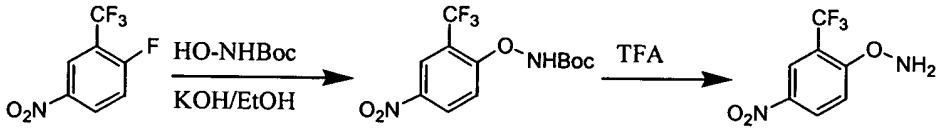
1 2 3 4

[0015] Sodium Hydride 60% dispersion in mineral oil (2.00g, 49.9mmol) was added to a stirred solution of ethyl hydroxyacetimidate **(2)** (4.29g, 41.6mmol) in DMF (100mL) at 0C under dry nitrogen atmosphere. After stirring at 0C for 15 minutes, 4-fluoro-2-nitrobenzotrifluoride **(1)** (8.70g, 41.6mmol) was added drop wise. The solution was stirred for an additional hour at 0C and allowed to slowly warm to room temperature. Ethyl acetate and water were added to quench the reaction. .The layers were separated and the organic layer was washed with sat. NaCl solution, dried over sodium sulfate and concentrated. Purification on ISCO chromatography system using ethyl acetate/hexanes gradient gave 10.45g of **3**. NMR (CDCL3) δ s, 1H, 8.3; d, 1H, 7.9; d, 1H, 7.8; q, 2H, 4.2; s, 3H, 2.3; t, 3H, 1.4.

[0016] A 70% solution of perchloric acid (20mL) was added slowly to a stirred solution of **3** (10.45g, 43.2mmol) in dioxane (30 mL) at 0C. The reaction was stirred for an additional 1 hr and ethyl acetate was added. The solution was washed with water, 5% K_2CO_3, dried over sodium sulfate and concentrated. Purification on ISCO chromatography system using ethyl acetate/hexanes gradient gave 6.55g of **4**. NMR (CDCL3) δ s, 1H, 8.2; d, 1H, 78.0; d, 1H, 7.8; 3, 2H, 6.3.

Example 2

Synthesis of 4-nitro-2-(trifluoromethyl)phenylhydroxylamine



5 6 7

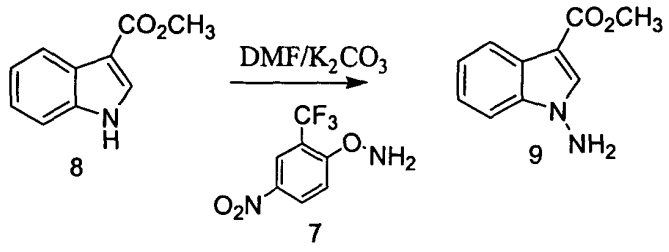
[0017] Solid KOH (4.8 g ,86.4 mmol) was added to 60 mL of ethanol and stirred until a clear solution resulted. To this solution was added 3.2 g (24.0 mmol) of Boc-hydroxylamine and the reaction mixture cooled to 0°C. To this reaction mixture, a solution of 5.0 g (30.0 mmol) of 2-fluoro-5-nitro-trifluromethylbenzene in 30 ml ethanol was added dropwise (30 min) and stirred at 0°C for 3 h. Diluted with water and extracted with ethyl acetate, dried and evaporated to give product **6** as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 7.61 (d, 1H), 7.95 (s, 1H), 8.45 (d, 1H), 8.61 (s, 1H).

[0018] **6** was dissolved in trifluoroacetic acid (30 mL) and the reaction mixture stirred at ambient temperature for 1 h. All starting materials disappeared as monitored by TLC (10% ethylacetate/hexane). trifluoroacetic acid was removed under vacuo. The solids dissolved in ethyl

acetate, washed with 10% sodium carbonate, dried and evaporated to give the product as a slightly yellow solid. Recrystallization from 10% hexane in ethyl acetate provided 4.3 g (80%) of phenylhydroxylamine **7** as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 2H), 7.42 (d, 1H), 8.41 (d, 1H), 8.51 (s, 1H).

Example 3

Amination of methyl indole-3-carboxylate



[0019] To a solution of indole **8** (175.2 mg, 1.0 mmol) in 3 mL DMF was added finely powdered K_2CO_3 (415.0 mg, 3.0 mmol) and stirred for 1 h. The aminating reagent **7** (288.0 mg, 1.3 mmol) was added all at once and the reaction mixture stirred for 24 h. Diluted with water and the product was extracted with ethyl acetate. The organic layer was dried and evaporated. The product was purified by silica gel column chromatography using 20% ethyl acetate in hexane to obtain 95 mg (50%) of product **9** as white solids MS (M+1 191).